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THE GERMPLASM AS A STEREOCHEMIC SYSTEM[1]

THE discovery in 1883 by Dr. S. Weir Mitchell and myself that the toxic principles of the venoms of serpents are albuminous marked an era in the chemistry, physiology and pathology of proteins, and among other things laid the foundation of our knowledge of bacterial and other toxalbumins. Since that time our information of the properties of albuminous substances, then extremely meager and somewhat chaotic, has greatly advanced, and many investigations have been made to determine the precise nature of these poisons, with the effect of more or less modifying the statements we then set forth. The astonishing fact that these terribly lethal substances were found by the tests of the day to be proteins, and that apart from their toxic properties they were indistinguishable from corresponding bodies that are ingested as food or derived therefrom by the processes of digestion, or found as normal constituents of the living tissues generally, naturally led me to much speculation and ultimately to the pursuit of the very elaborate series of researches that I have been carrying on during the past decade under the auspices of the Carnegie Institution of Washington, reports of two of which have appeared as Publications Nos. 116 and 173.

It would be futile for me to attempt within the necessarily restricted time that can reasonably be allotted to the reading of a communication to present in a satisfactory form even the briefest summary of the very voluminous results and conclusions that are embodied in these works, or even an outline of

[1] Read by title at the meeting of the American Philosophical Society, April 25, 1914, and in full before the Society of Normal and Pathological Physiology of the University of Pennsylvania, April 28, 1914.

their bearings upon a vast number of problems of normal and abnormal biology, so that perforce my remarks shall be limited to a fragment—a fragment which bears upon one of the most baffling yet all-absorbing problems of life, why "like begets like."

A. The Specificity of Stereoisomerides in Relation to Genera, Species, etc.

These researches have as their essential basis the conception that *in different organisms corresponding complex organic substances that constitute the supreme structural components of protoplasm and the major synthetic products of protoplasmic activity are not in any case absolutely identical in chemical constitution, and that each such substance may exist in countless modifications, each modification being characteristic of the form of protoplasm, the organ, the individual, the sex, the species and the genus.* This conception was supported not only by the extraordinary differences noted between the albuminous substances of venom and those of other parts of the serpent, but also by the results of the investigations of Hanriot, who described marked differences in the properties of the lipases of the pancreatic juice and the blood; of Hoppe-Seyler and others who stated that the pepsins of cold- and warm-blooded animals are not identical; of Wróblewsky and others who recorded differences in the pepsins of mammals; of Kossell and his students who found that the protamins obtained from the spermatozoa of different species of fish are not identical; and of various observers who have noted that the erythrocytes of one species when injected into the blood of another are in the nature of foreign bodies and rapidly destroyed. During subsequent years, and especially very recently, data have been rapidly accumulating along many and diverse lines of investigation which collectively indicate that every individual is a chemical entity that differs in characteristic particulars from every other. To any one familiar with the advances of biochemistry and with the trend of scientific progress towards the explanation of vital phenomena on a physico-chemical basis, it will be obvious that if the conception of the non-uniform constitution of corresponding proteins and other corresponding complex organic substances in different organisms and parts of organisms were found to be justified by the results of laboratory investigation a bewildering field of speculation, reasoning and investigation would be laid open—a field so extensive as to include every domain of biological science, and seemingly to render possible, and even probable, a logical explanation of the mechanisms underlying the differentiation of individuals, sex, varieties, species and genera; of the causes of fluctuations and mutations; of the phenomena of Mendelism and heredity in general; of the processes of fecundation and sex-determination; of the tolerance of certain organisms to organic poisons that may be extremely virulent to other forms of life; of tumor formation, reversions, malformations and monsters; of anaphylaxis, certain toxemias, immunities, etc.; and of a vast number of other phenomena of normal and abnormal life which as yet are partially or wholly clothed in mystery.

Some years previous to the discovery of the nature of the lethal constituents of venoms, Pasteur found that there exist three kinds of tartaric acid which, because of different effects on the ray of polarized light, are distinguished as the dextro-, lævo- and racemic-tartaric acids, the dextro form rotating the ray to the right, the lævo form to the left, and the racemic form not at all. When these acids were subjected in separate solutions to the actions of *Penicillium glaucum* fermentation proceeded in the dextro form, but not in the lævo form, while in the solution of the racemic acid, which is a mixture of the dextro and lævo acids, the dextro form disappeared, leaving the lævo moiety unaffected. All three acids have the same chemical composition and chemical properties, but differ strikingly in their effects on polarized light and in nutritive properties. Identical or corresponding peculiarities have since been recorded in relation to a large number of substances. Thus, of the twelve known forms of hexoses, or glucoses, only the dextro forms are fermentable,

that is, capable of being used by certain low organisms as food, but not all are thus available, and, moreover, those which are show marked differences in the degree of fermentability. In the case of other substances *Penicillium* may consume the lævo form, but not the dextro form. Other organisms show similar selectivities, using either dextro or lævo form, or both, but in the latter case in unequal degree. Even more striking instances have been recorded in the actions of poisons, as, for instance, dextro-nicotine is only half as toxic as the lævo form; dextro-adrenalin has only one twelfth the power of the lævo form; racemic-cocaine has a quicker and more intense but less lasting action than the lævo form; the asparagines, hyoscines, hyoscyamines and other substances have been found to exhibit marked differences in accordance with variations in their optical properties. With other bodies belonging to this category it may be found that one form is sweet while another is tasteless; another may be odorous, but its enantiomorphous form without odor.

To the foregoing there may be added examples of other substances that exist in several forms, but which physico-chemically belong to a different class. Thus, nitroglycerine may exist in forms that are so different that under given conditions of temperature and percussion one is explosive and the other non-explosive. Differences in substances which are found in allotropic forms may be as marked as in any of the preceding illustrations, as, for instance, in the case of phosphorus, which is familiar as the yellow, white, black and red varieties, all of which with the exception of red phosphorus are exceedingly poisonous, while the latter is inert. The ortho, meta and para forms of a given substance may exhibit more or less marked physiological and toxicological variations, and so on.

The explanation of the remarkable differences shown by these substances, which differences are paralleled by those manifested by the lethal and innocuous proteins of the serpent, the pepsins, the protamins and the red blood corpuscles is to be found in the results of two independent but intimately related lines of physico-chemical research: (1) The investigations of Van't Hoff and LeBel and subsequent observers which have laid the foundation of a new, and to the biologist and physician an extraordinarily important, development of chemistry known as stereochemistry—a department that treats of the arrangements of the atoms, groups and masses of molecules, or in other words of intramolecular arrangement or configuration of molecular components in the three dimensions of space. (2) The investigations of Willard Gibbs and others which have given us the "phase rule," which defines the phases or forms in which a given substance or combination of substances may exist owing to differences in intramolecular and extramolecular arrangements and concentration of their components in relation to temperature and pressure.

According to stereochemistry a given substance may exist in multiple forms dependent upon differences in the configuration of the molecule, all of which forms have in common the fundamental chemical characteristics of a given prototype, yet each may have certain properties which positively distinguish it from the others. Theoretically, such substances as serum albumin, serum globulin, hemoglobin, starch, glycogen and chlorophyl may be produced by nature in countless modified forms, owing to differences in intramolecular arrangements. Miescher has estimated that the serum globulin molecule may exist in a thousand million forms. Substances that exist in such multiple forms of a prototype are distinguished as stereoisomers. The remarkable fact has been noted by Fischer and others that stereoisomers may exhibit as great or even greater differences in their properties than those manifested by even closely related isomers, which latter in comparison with stereoisomers are distantly if at all chemically related. As already instanced, so slight a change in molecular configuration as gives rise to dextro and lævo forms may be sufficient to cause definite and characteristic and even profound differences in physical, nutritive and physiological properties.

In accordance with the "phase rule" a sub-

stance or a combination of substances may exist in the form of heterogeneous or homogeneous systems, a heterogeneous system consisting of a number of homogeneous systems, each of which latter is a manifestation of an individual phase and distinguishable from the others by physical, mechanical, chemical or physiological properties. The number of phases of a heterogeneous system increases with the number of component systems, and the number of the latter is in direct relationship to the number of independent variable constituents. Therefore, by means of variations of either or both intramolecular or extramolecular arrangement the number of forms of a substance or combination of substances may range from few to infinite.

Our means of differentiating stereoisomers are, on the whole, limited, and for the most part crude, and while it has been found that differences so marked as those referred to may be detected by the ordinary procedures, it seems obvious that the inherent limitations of such methods render them inadequate where a large number of stereoisomerides or related bodies which may exhibit only obscure modifications are to be definitely differentiated, so that other and more sensitive methods must be sought, or at least special methods that are adapted to exceptional conditions. The results of much preliminary investigation in this direction led in one research to the adoption of the crystallographic method, especially the use of the polarizing microscope, which in its very modern developments of analysis has demonstrated that substances which have different molecular structures exhibit corresponding differences in crystalline form and polariscopic properties; and, moreover, that the "optical reactions" may be found to be as distinctive and as exact analytically as the reactions obtained by the conventional methods of the chemist. Furthermore, the necessities of the hypothesis demanded the selection of a substance for study of a character which upon theoretical grounds might be expected to exist in nature widely distributed and readily procurable, and, as a consequence, hemoglobin was selected.

In the investigation of the hemoglobins I had as a coworker Professor Amos Peaslee Brown. Hemoglobins were examined that were obtained from over 100 animals, representing a large variety of species, genera and families. From the data recorded certain facts are especially conspicuous, among which may be mentioned the following:

1. The constant recurrence of certain angles, plane and dihedral, in the hemoglobins of various species, even when the species are widely separated and the crystals belong to various crystal systems. This feature indicates a common structure of the hemoglobin molecules, whatever their source.

2. The constant recurrence of certain types of twinning in the hemoglobins, and the prevalence of mimosie. This has the same significance as the foregoing.

3. The constancy of generic characters in the crystals. The crystals of the various species of any genus belong to a crystallographic group. When their characters are tabulated they at once recall crystallographic groups of inorganic compounds. The crystals of the genus *Felis* constitute an isomorphous group which is as strictly isomorphous as the groups of rhombohedral and orthorhombic carbonates among minerals, or the more complex molecules of the members of the group of monosymmetric double sulphates.

4. The crystallographic specificity in relation to species. The crystals of each species of a genus, when they are favorably developed for examination in the polarizing microscope, can usually be distinguished from each other by definite angles and other properties, while preserving the isomorphous character belonging to the genus. Where, on account of difficulty of measurement, the differences can not be given a quantitative value variations in habit and mode of growth of the crystals often show specific differences.

5. The occurrence of several types of oxyhemoglobin in members of certain genera. In some species the oxyhemoglobin is dimorphous and in others trimorphous. Where several types of crystals occur in this way in the species of a genus the crystals of each type

may be arranged in an isomorphous series. In other words, certain genera as regards the hemoglobins are isodimorphous and others isotrimorphous.

6. When orders, families, genera or species are well separated the hemoglobins are correspondingly markedly differentiated. For instance, so different are the hemoglobins of *Aves, Marsupialia, Ungulata* and *Rodentia* that there would be no more likelihood of confounding the hemoglobins than there would be of mistaking the animals themselves. Even where there is much less zoological separation, as in the case of the genera of a given family, but where there is well-marked zoological distinction, the hemoglobins are so different as to permit readily of positive diagnosis. When, however, the relationships are close the hemoglobins are correspondingly close, so that in instances of an alliance such as in *Canis, Vulpes* and *Urocyon,* which genera years ago were included in one genus (and doubtless correctly) the hemoglobins are very much alike, and in these cases they may exhibit closer resemblances than may be found in general in specimens obtained from well-separated species of a genus.

So distinctive zoologically are these modified forms of hemoglobins that we had no difficulty in recognizing that the common white rat is the albino of *Mus norvegicus* (*Mus norvegicus albus* Hatai) and not of *Mus rattus,* as almost universally stated, and that Ursidæ are related to Phocidæ (as suggested by Mivart 30 years ago), but not to Canidæ, as stated in modern works on zoology. Moreover, we were quick to detect errors in labeling, as, for instance, when a specimen marked as coming from a species of *Papio* was found to belong to one of the Felidæ. Generic forms of hemoglobin when obtained from well-separated genera are, in fact, so different in their molecular structures that when any two are together in solution they do not fuse to form a single kind of hemoglobin or a homogeneous solution, but continue as discrete disunited particles, so that when crystallization occurs each crystallizes independently of the other and without modification other than that which is dependent upon such incidental conditions as are to be taken into account ordinarily during crystallization. Thus, the hemoglobin of the dog crystallizes in rhombic prisms which have a diamond-shaped cross-section; that of the guinea-pig in tetrahedra; that of the squirrel in hexagonal plates; and that of the rat in elongated six-sided plates. When any two of these hemoglobins are together in solution and crystallization occurs, each appears in its own form. Such phenomena indicate that the structures of the hemoglobin molecules are quite different; in fact, more differentiated than the molecules of members of an isomorphous group of simple carbonates, such as the carbonates of calcium and magnesium which when in separate solutions crystallize in rhombohedrons whose corresponding angles differ 2° 15′, but which when in molecular union, as in the mineral dolomite, crystallize as a single substance which has an intermediate angle.

Upon the basis of our data it is not going too far to assume that it has been satisfactorily demonstrated theoretically, inferentially and experimentally that at least this one substance (hemoglobin) may exist in an inconceivable number of stereoisomeric forms,[2] each form being peculiar to at least genus and species and so decidedly differentiated as to render the "hemoglobin crystal test" more sensitive in the recognition of animals and animal relationships than the "zooprecipitin test."

Subsequent to the research referred to investigations have been pursued in the study of hemoglobins from various additional sources, especially from representatives of *Primates,* with the result in the latter case of finding indubitable evidence of an ancestral alliance of man and the man-like apes.

More or less elaborate studies by crystallographic and other methods have also been made with other albuminous substances and with starches, glycogens, phytocholesterins, chlo-

[2] Even if we assume that the different forms are not, strictly speaking, stereoisomers it must be admitted that hemoglobin exists in forms that are specifically modified in relation to genera and species.

rophyls and other complex synthetic products of animal and plant life, especially with starches, of which over 300 specimens were examined that were obtained from different plant sources, including representatives of a considerable number of families, genera, species, varieties and hybrids. In all of these investigations the results are not only in full accord with those of the hemoglobin researches but also in some instances of broader significance because by better methods of differentiation in some cases it was found possible to recognize not only peculiarities as regards genus or species, but also varieties and hybrids, and even to trace in hybrids with marked definiteness the transmission of parental characteristics.

Summing up the results of these independent but interwoven researches, we find that the modified forms of each of these substances lend themselves to a very definite system of classification, and to one that is in general accord with that of the botanist and zoologist, that is, each genus is characterized by a distinctive type of hemoglobin, albumin, starch, etc., as the case may be, which may be designated the generic-type; every species of the genus will have a modification of this type, which is a species-type, or generic primary sub-type; and every variety of a species will have a modification of the species-type, that is a variety-type, or generic secondary sub-type, or species sub-type. In fact, it seems clear that with revisions of present classifications that are certain to come there will be found definite family types; and, moreover, that with improved methods of differentiation there will be discovered positively distinctive sex- and individual-types. This last statement already has support in the results of collateral lines of research which bear upon the specificities of enzymes, anaphylaxis, precipitin reactions, immune sera, etc.

From the foregoing data it seems obvious that *the complex organic substances which may be assumed to constitute the essential fundamental constituents of protoplasm and the immediate complex synthetic products of protoplasmic activity may exist in exceedingly numerous or even countless stereoisomeric forms, each form being peculiarly and specifically modified in relation to genus, species, variety, race, sex, individual or even part of an individual.*

B. Protoplasm a Complex Stereoisomeric System

The next logical step in our investigation is manifestly the study of the bearings of these stereoisomers, as such and in their variable combinations and associations, upon the structure, processes and products of protoplasm. Protoplasm according to the modern developments of biochemistry is to be regarded as being in the nature of an extremely complex, labile aggregate of proteins, fats, carbohydrates and other substances that are peculiarly associated to constitute a physico-chemical mechanism. The possible number of "phases" in which such a system can exist varies with the forms of the stereoisomerides and in general with the number and independent variability of the components. In such a mechanism we conceive that the number of variables is inconceivably great. From analogy we believe that such mechanisms are so extremely sensitive that the properties and processes may be modified by even so slight a change as the substitution of one form of stereoisomeride for another of the same prototype. Were it practicable to examine all of the most complex of the organic structural components of protoplasm, it doubtless would be found that every one exists in a form that is peculiar to the individual and his position in classification. Moreover, we must conceive that the components of protoplasm are as specific in relation to the form of protoplasm as are the peculiar forms of stereoisomers, so that different forms of protoplasm are characterized physico-chemically (1) by the peculiarities of the stereoisomerides, and (2) by the peculiarities of the kinds, combinations, associations and arrangements of the components in the three dimensions of space.

In accordance with the foregoing the human organism may be regarded as being a highly organized composite of heterogeneous physico-

chemical systems that are composed of a vast number of parts, each such part representing a particular "phase" of the system and being physically, mechanically, chemically and functionally an individual interacting unit of the aggregate. Hence, it follows that the sum or totality of these peculiarly modified stereoisomers *per se,* and of their arrangements with the associated components, constitutes a "stereochemic system" that is peculiar to the cell; that the sum of the cell-systems is peculiar to the tissue; that the sum of the tissue-systems is peculiar to the organ; and that the sum of the organ-systems is peculiar to the individual.

While the living organism had been for years recognized as being in the nature of an exceedingly complex physico-chemical aggregate of interacting independent and interdependent parts that constitute a single working unit, it has been in only recent years that the mechanisms that bring about cooperative activities of the various parts has been made clear. The governing influences of the nervous system were found inadequate even in the highest organisms, not to speak of forms of life in which such actions occur, but in which there is apparently a total absence of nervous matter. As an associate of the nervous system, and doubtless far antedating it in organic evolution, is a correlative mechanism of a chemical character that is of the greatest importance, and doubtless equally so throughout the whole range of living organisms from the lowest to the highest. Every living cell, whether it be in the form of a unicellular organism or a component of a multicellular organism, is undoubtedly in the nature of a heterogeneous stereochemic system, each of the component parts of the system forming substances which may affect directly or indirectly the activities of the processes of the other parts; likewise every cell of a multicellular organism is not only in itself a heterogeneous system, but a part of a number of associated heterogeneous systems and which by virtue of certain of its products, with or without the agency of the blood-vascular or lymph-vascular systems, may exercise influences upon other structures, which structures may have or seemingly not have either structural or physiological relationship. Thus we find that a secretin formed in the pyloric glands of the gastric mucosa may excite the glands of the cardia; that growth is determined by some product or products of the pituitary body that are carried to the various structures; that the liver, pancreas and intestinal glands are excited to secretory activity by a peculiar substance formed in the duodenal and jejunal mucosæ; that carbohydrate metabolism in the liver and muscle is influenced to a profound degree by hormones that are formed in the pancreas; that lactation is determined essentially by substances derived from the corpus luteum, placenta and involuting womb; that the periods of ovulation and menstruation are inhibited by secretins of the corpus luteum; that vitally important states of activity of the generative organs are directly associated with functions of the adrenal glands; and that normal development, especially of secondary sexual characters, is intimately related to the ovaries and testicles. To these extraordinary correlations might be added many others. Some of the bodily structures are in this way so definitely associated in their activities as to constitute cooperating or interacting systems, so that the tissue products are complementary, supplementary, synergistic or antagonistic in their influences upon given structures. Such correlations must be, for perfectly obvious reasons, one of the most primitive forms of interprotoplasmic correlation, and we are justified, upon the basis of our present knowledge, in the conclusion that each active part of a cell, each cell, each tissue and each organ contributes products which may affect the activities of functionally related or unrelated parts. Hence would follow the dictum that *not only is every part of a cell, every cell, every tissue and every organ an individualized stereochemic unit, but also that its operations, and hence the nature of its products, must be subject directly or indirectly to the influence of every other active part of the organism, however different the structures and functions may be.*

C. The Germplasm a Stereochemic System, that is, a Physico-chemical System that is Particularized by the Characters of its Stereoisomers and the Arrangements of its Components in the Three Dimensions of Space

If during the progress of development there arise the multiple forms of differentiated protoplasm that are represented in the nerve cells, muscles, glands, etc., which exhibit such diversity of form, functions, composition and products, each part being correlated to other parts by the agency of tissue products, it is logical to assume that in the development of the ovaries and testicles these organs have been so specialized as to endow them with the attribute of producing a form of protoplasm that embodies in a germinal state the fundamental peculiar stereoisomerides and the peculiar arrangements or phases of the associated proteins, fats, carbohydrates and other substances which inherently characterize the organism; and, moreover, that owing to the influences of the products of activity of the various tissues upon these organs, such changes in the organism as give rise to acquired characters may through the actions of modified or new tissue products or foreign substances affect the operations of these organs and thus alter the germplasm and consequently become manifested in some form in the offspring. The ovule in its incipiency is conceived to be comparable to a complex unequilibrated solution in which changes go on until the attainment of full development, at which time it is equilibrated and remains inactive because of the absence of some disturbing influence, but in which energy-reactions may be initiated physically, mechanically or chemically, and proceed according to definite physico-chemical laws in definite directions to a definite end. As, for instance, when a solution of boiled starch and diastase is at a temperature below the minimal of activity and the temperature is raised, causing immediate developmental activation; or when the equilibrated molecules of nitroglycerine are exploded by percussion; or when an equilibrated maltose-dextrose-maltase solution is rendered active by dilution with water.

The *nature of the germplasm* or transmissive material that serves as the bridge of continuity between parents and offspring has been the subject of speculation from time immemorial. Such hypotheses and theories as have been advanced have had reference almost wholly to its physical constitution or ultimate morphological structure. Most of them are micromeric, that is, they hold that the germplasm is made up of infinite number of discrete ultramicroscopic particles which are endowed with both determinate structural and vital attributes. A considerable degree of ingenuity has been displayed in their formulation. Thus, we have the "organic molecules" of Buffon, the "microzymes" of Bèchamp, the "life units" of Spencer, the "plastidules" of Maggi, the "bioplasts" of Altmann, the "stirps" of Galton, the "gemmules" of Darwin, the "biophors" of Weismann, the "pangens" of DeVries, etc., each author attributing to the units certain inherent peculiarities. To the foregoing might be added particularly the conceptions that belong to the chemical category, such as the "chemism" of LeDantec and the "physico-chemical" theory of Delage. Some of these conceptions are so fanciful in the light of modern science as to be unworthy of more than passing consideration, while none of them has led anywhere beyond the field of speculation and reasoning. Even the very recent and extremely interesting and important additions to our knowledge of the histological phenomena of the developing ovum, especially of the chromosomes, have not taken us appreciably nearer the ultimate constitution or mechanism of the germplasm, or even to the nature of the reactions which occur immediately antecedent to and cause the formation of the chromosomes.

A theory to be *ideal* must not only have as its basis well-defined principles that are consistent with facts, but also be capable of substantiation by laboratory investigation. Given as the basis of scientific study a germplasm that has inherently the power of development; that is in the form of a stereochemic system that is peculiar to the organism; that is highly impressionable to stimuli; and that has the

marked plasticity that is inherent to organic colloidal matter, we have all the postulates that are needed as a foundation upon which, according to the laws of physical chemistry, can be built a logical explanation of the essential fundamental elements of the mechanism of heredity.

The *inherent potentiality* that determines the development of the egg along a line of definite sequential processes must be recognized as being common to both animate and inanimate matter and subject to the same laws, so that the phenomena of living and dead matter are inseparably linked and reciprocally explanatory. The typical condition of matter of definite composition is crystalline, and the crystalline form is the result of development that becomes manifested in a separation and orderly and progressive arrangements of components in the three dimensions of space. Having a homogeneous solution of various selected crystalline substances of appropriate chemical composition and constitution, and given conditions attendant to crystallization, the successive stages of crystalline development will proceed along fixed and definitely recognized lines, and the interactions and interaction-relationships between the various substances constituting the physico-chemical mechanism become obvious to a greater or less extent in the peculiarities of form, composition and other properties of the crystals. Having in the germplasm an analogous physico-chemical system, but one which is markedly different especially because of its organic and colloidal character and infinitely greater molecular complexity and sensitivity, the phenomena of development likewise proceed in conformity with the same laws along definite lines, but they are for perfectly manifest reasons more complex and varied, more difficult of analysis, and necessarily in many very important respects quite different. Each step in this orderly development leads not merely to changes of the physico-chemical mechanism by the modification, rearrangement, or splitting off of component parts, but also to alterations which automatically determine the characters of the next succeeding step, and so on to the establishment of physico-chemical equilibrium and the consequent termination of the reactions.

In living matter the chemical processes are dependent to a preeminent degree upon enzymes that are formed by the different kinds of protoplasm to serve as implements to carry out operations that are essential to their existence, and such enzymes are modifiable in quantity and quality in accordance with changes in internal and external conditions. The nature of both reactions and products of enzymic action depends upon the constitution and composition of the physico-chemical mechanism of which the enzyme is an integral part. Whether or not at each step of serial reactions a portion of preexisting enzyme is merely modified or a new enzyme is formed which constitutes an essential part of the particular phase of the reactions is not known, but that one or the other occurs is apparently without question. It has long been established that some of the lower organisms, such as the yeast plant, have the property of modifying the characters of the enzymes produced in relation to varying conditions; recent studies of the animal organism show that the same phenomenon occurs in both tissues and blood; and our knowledge of the processes concerned in the catabolism and anabolism of complex substances, such as starch, is fully in support of such a conception. In other words, as each step of development is reached the alterations which occur in the physico-chemical mechanism absolutely automatically predetermine the characters of the changes of the next succeeding step, and so on to the end. Hence it follows that the peculiarities of any given physico-chemical mechanism predetermine the characters of the phenomena which ensue under given conditions.

An illustration of the probable *modus operandi* of such a mechanism is found in the phenomena of the synthesis and analysis of starch: During the production of starch through the agency of the chloroplast or leucoplast we conceive that there are instituted a predetermined, orderly, independent and interdependent series of reactions, the first

of which is manifested in an interaction between water and carbon dioxide through the agency of an enzyme in the form of an oxidase to form formaldehyde. During this process there is formed another enzyme, which tentatively may be designated an aldehydase, that reacts with formaldehyde and by polymerization and condensation of six molecules gives rise to a simple sugar, such as dextrose. At the same time another enzyme appears in the form of maltase, which, reacting with the dextrose causes the formation of maltose, during which reaction another enzyme, a dextrinase, is produced which reacts with the maltose to yield dextrin. Going on with this reaction, another enzyme which may be designated an amylase appears, which, reacting with the dextrin, forms soluble starch. During this stage there arises another enzyme, a coagulase, which converts the starch from the soluble to the insoluble form or ordinary starch. At this stage the series of reactions have reached their end because a state of physico-chemical equilibrium has become established, the ultimate purpose of the processes being attained; that is a form of pabulum of extremely high nutritive value and of extremely low molecular pressure, even in soluble form, so that it may entirely and rapidly disappear without disturbance of physico-chemical equilibrium in the starch-bearing cells. The mechanism concerned in starch-formation is without doubt paralleled in the synthesis of proteins, fats and other complex organic substances, and it is but a step from the individual serial processes concerned in the formation of each of these substances to associated processes whereby there are formed and combined the various substances that constitute the organic structural components of protoplasm. Moreover, such serial processes are reversible at any stage, and so simple a modification as a change in the per cent. of water may, as in the maltose-dextrose-glucase reaction, cause a synthetic change.

In vitro in both synthetic and analytic processes like those which constitute serial steps in the building up and breaking down of starch, protein, fat and other complex organic substances there does not occur in any reaction, as far as known, either a transformation or a production of enzyme such as occurs *in vivo,* hence, when a single enzyme is present it carries out but one step of the reactions, but when, as in the case of diastases as ordinarily prepared, the enzyme is not a single substance or unit body but a composite of a number of enzymes or modifications of a given basic enzyme, serial steps may occur as *in vivo.* Thus, if only a single enzyme be present formaldehyde may be converted into a monosaccharose, or a monosaccharose into a disaccharose, or a disaccharose into a polysaccharose such as dextrin, or dextrin into a higher form of polysaccharose such as soluble starch, according to the enzyme or modified enzyme and initial substance present; or the reverse of any one of these processes may occur if proper conditions are present, but never do any two successive progressive or regressive steps occur unless through the agency of two different or modified forms of enzymes which are present.

It will thus be apparent that the first step of synthesis is determined by the character of the initial physico-chemical mechanism and that all subsequent reactions under given conditions are definitely predetermined; in other words, the entire train of reactions depends inherently upon the nature of the initial physico-chemical mechanism of which the enzyme that starts the serial changes is an integral part.

Having a specific stereochemic system, such a system in accordance with the laws of physical-chemistry can exist in either a latent or active state, and that when in an active state the reaction or reactions are always in the direction of the establishment of equilibrium of solution, every reaction or series of reactions being as definitely predetermined as is every reaction familiar to the inorganic chemist. The germplasm in the form in which it is secreted may be regarded as being in the nature of an exceedingly complex stereochemic system which is from its incipiency, or very soon is in a state of physico-chemical unequilibrium, and in which, as a consequence,

reactions are set up which are manifested especially in histological developments that ultimately characterize the fully developed ovule, at which time a state of physico-chemical equilibrium is established, as is evident by the arrested developmental activities. This state of physico-chemical equilibrium of the matured ovule may be instantly changed to one leading to serial definitely predetermined reactions by means of an activating substance or condition, such as certain ions or inorganic salts, a spermatozoon, or a needle prick, by initiating the first step of the reactions, the nature of the succeeding reactions being predetermined primarily by the inherent nature of the physico-chemical system and secondarily by the factor that activates it. In other words, from this initial stereochemic system there arises a complex heterogeneous system that ultimately is morphologically expressed in the histology of the matured ovule and from which are formed a composite of correlated, independent, interdependent and differentiated masses which represent different phases of the components of the initial system which have been modified not only physico-chemically as expressed by changes in physical, mechanical and chemical properties, but also in developmental energies; and from this composite are developed successively other systems.

Owing to the *great impressionability and plasticity* of such an exceedingly complex stereochemic system as the germplasm, it follows that the germplasm must be extremely sensitive to changes in internal and external conditions, and that its operations and products may be so materially modified by changes in its molecular arrangements or components as to give rise to variables that are manifested in the transmutability of sex, variations, fluctuations, mutations, deformities, retrogressions, tumor formation, immunities, etc.

Assuming in accordance with our conception that the germplasm is in its incipiency an unequilibrated stereochemic system that is characteristic of the inherent, fundamental stereochemic system of the parent, it follows, as a corollary that, having a highly specialized form of parental structural material with peculiar energy-properties, the offspring must of necessity possess essentially the same fundamental characteristics as the parents when normal fecundation has occurred, and that it would be quite as impossible to have any other result than in ordinary chemical reactions under given conditions of experiment. The essential characters of the building material as regards substances, arrangements and energy-properties are definitely fixed within narrow limits of variation.

That the peculiar forms of stereoisomerides or intimately related bodies that are inherent in the parent are conveyed in the germplasm to the offspring, and hence of necessity serve to distinguish a given form of germplasm from that of any other species or genus, and that the stereochemic conception of the nature of the germplasm is capable of laboratory demonstration, are instanced in the results of the investigations of Kossell and his students who found that simple forms of protein, known as protamins, obtained from the spermatozoa of different species of fish are different, each being apparently of a form peculiar to the source. Here is one substance at least that seems to be in specific stereoisomeric forms in the sperm of different species, which obviously must affect the properties of the germplasm, and which when brought in contact with the germplasm of the egg play its part in determining the phenomena of development. Moreover, by the "precipitin reaction" method Blakeslee and Gortner have found evidence that is consistent with the conclusion that there are not only "species proteins" but also "sex proteins," and this receives support in a number of very recent investigations, especially those of Steinach, who found that the corresponding hormones secreted by the ovaries and testicles are different, and that by virtue of these differences the secondary sexual characters, female and male, are determined. Thus he found in castrated young males, in which transplantation of ovaries had been practised, that the development of masculine peculiarities is inhibited and female traits substituted, so that the individuals tend to assume the

female type and become to a striking degree feminized-males, as shown in bodily form, in a development of the mammary glands, in lactation, and in an alteration of psycho-sexual characters. Furthermore, Riddle has found that the ova of the pigeon are dimorphic, one males and the other half females; that the eggs having the male tendency have a higher per cent. of water, a smaller size, and a lower half having an inherent tendency to produce males and the other half females; that the eggs having the male tendency have a higher per cent. of water, a smaller size, and a lower per cent. of potential energy; and that the "sex-foundation" of the germplasm is transmutable, so that an egg that has inherently the male tendency may become female, and that such females exhibit secondary male sexual characters. The transmutability of the germplasm is comparable in its physico-chemical mechanism to the reversion of the maltose-dextrose-maltase reaction that is caused by a change in concentration of the solution, the dextrose being reverted into iso-maltose and not to the antecedent maltose—the male egg is not changed into a female egg, but into a modified or feminized-male egg.

In considering the transmissibility of parental substances it is essential to distinguish positively between the stereoisomerides and intimately related bodies that are *inherent* in the parent and those which are *acquired* through infection or otherwise. Thus antibodies that are acquired by the mother may be without influence upon the ovary during the formation of the germplasm and not even become a constituent of the latter. On the other hand, an immunity may be established in the mother that may be conveyed to the offspring, yet, curiously enough, such an immunity may not be transmitted by the immunized male. In processes of the production of the germplasm the ovary may be as insensitive to the presence of many acquired substances of the blood as are some or all other organs, and there is no more reason in general for expecting the ovary and its product to be affected by such bodies or conditions than there is for the pancreas and the pancreatic juice or any other secretory structure and its product to be affected. Every acquired substance must in its relations to the ovaries be governed by the same physico-chemical laws as determine specific selectivities or reactivities in connection with the tissues generally. Hence, any such substance may be reactive in relation to one structure, but not to another.

Plasticity as regards sex-determination has been demonstrated in the studies of the development of a male (drone) bee from the unfertilized egg, and of a female from the fertilized egg. Moreover, the developing female bee when fed on ordinary food becomes a common female "worker," but when fed on royal food develops into a queen.

The *continuity of the building material* between parent and offspring is seen in its simplest manifestations in reproduction among protozoa by binary fission and budding, by which the part separated from the parent mass is in all essential respects like the parent, having the same fundamental physico-chemical composition and constitution. That in such instances the offspring should be a segmental counterpart of the parent mass seems as obvious as that halves of a cube of sugar should be alike. Similarly, if we have in the ovule and sperm forms of protoplasm which as stereochemic systems are in all fundamental respects counterparts of those from which the parents were developed, it follows that the offspring must under normal conditions in accordance with the laws of physical chemistry have the same fundamental parental characteristics, as much so as separated portions of any complex stereochemic system must possess the properties of the initial mass. Moreover, if the stereochemic systems of germplasms of the female and male differ, as must be admitted, it is manifest that the stereochemic system of the egg that has been activated artificially or naturally, as the case may be, must be different, and hence undergo development differences that will be obvious in the offspring. In the first instance, the serial reactions which lead to the formation of the different tissues, etc., are activated by a mere disturbance of physico-chemical equilibrium, which may be due to the conversion of a proenzyme into enzyme or a prosecretin to a secretin, or in

other words of an inactive body into an active one. In the second instance, there is not only activation, but the extremely important addition of the male stereochemic system which by admixture with the female system constitutes a female-male system. Therefore, in the first place the offspring is developed solely from the female stereochemic system, and in the second place from the combined female and male systems, one or the other of which may be wholly or in part dominant in determining certain peculiarities in the developmental changes. Moreover, owing to the transmutability of stereoisomerides and the multiphase transmutability of stereochemic systems, coupled with the reversibility of metabolic processes which may be due to even the simplest of changes in physico-chemical mechanisms, we have a logical basis for the explanation of the phenomena of sexual dimorphism that is expressed in the so-called male and female ova, and male and female spermatozoa; of primary and secondary hermaphroditism; of paradoxical sex developments where the unfertilized egg develops into either male or female offspring; and of sexual transmutability of the inherently male or female ovule.

It follows upon the basis of our theory that because of the inherent peculiarities of the stereochemic systems of the germplasms and the definitely predetermined nature of the entire series of reactions in accordance with the laws of physical chemistry that "like begets like" because like every other physico-chemical phenomenon, individual or serial, under given conditions, it is *a physico-chemical fatality.*

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THE CONTENT AND STRUCTURE OF THE ATOM[1]

THIS lecture has presented to you a vision of the recent struggle toward a better knowledge of the atom. Both experimental results and theory have been briefly discussed. You can readily place confidence in the former, but in the realm of theory you are unable to distinguish truth from error. I have brought to you, then, not the satisfaction which one enjoys in believing he hears the final truth, but rather the discontent with which the scholar views the limitations of knowledge in his field. Such discontent gives birth to zealous endeavor to learn new truth and is thus the precursor of that research in science which our society is organized to encourage. An attempt to think in sub-atomic terms very quickly makes one conscious of the limitations of our knowledge. But I wish to emphasize that such limitations occur in all sciences and, indeed, at any point that a scholar chooses to make his special study. These limitations are not usually easy to extend, especially in the older sciences. And just such difficulties furnish the challenge of scholarship in science to the young men and young women of ability.

There is, however, no need to offer explanations to those who are dissatisfied with a discussion in which truth and error can not be separated. The unscientific mind possesses but two compartments, one for truth and one for error, and such a mind has no compartment in which to place a discussion of the nature and structure of an atom. The scientist, however, recognizes no such compartments, for absolute truth and absolute error are unknown to him. After weighing the evidence furnished, his decisions consist only in selecting the degree of his confidence that is merited by that evidence.

Having given you a bird's-eye view of the evidence, it may now be appropriate to present a brief résumé in perspective of the great achievements in science which have been the subject of this lecture. We can now regard the existence of the sub-atomic electron with as much confidence as that given any other experimental fact in physics. There is yet a question as to whether or not the electron actually is our smallest unit of negative electricity, but the affirmative evidence is much the greater. The mass of the electron can be called "apparent," with the restriction that we know this to be true only to the de-

[1] The closing portion of the address of the retiring President of the Iowa Chapter of Sigma Xi, delivered on October 14th.